High frequency of somatically acquired p53 mutations in small-cell lung cancer cell lines and tumours.

D'Amico et al. — Oncogene 1992, 7: 339-46

INTRO

SCLC ≙ 25%

NSCLC ≙ 75%

Generally genetic abnormalities e.g caused by smoking but some evidence of a heredity component.

Analyses of mutations in p53 gene.

Chromosome 17p13.1 ⇒ nuclear phosphoprotein 53kDa. like transcription factors.

Aims: - 1. to determine frequency type and location of mutations throughout the p53 ORF in SCLC and compare with previous NSLC and other types.

2. compare freq of p53 mut bet SCLC cell lines and uncultured tumor specimens;

3. test whether p53 mut. are found in constitutional DNA of SCLC patients, which would indicate an inherited predisposition

RESULTS

cDNA (cloned DNA?) - all 16 had mutations in p53

Frequent occurrence of G-T transition

No common link with prognosis or treatment response

Mutation largely occurring somatically as adjacent normal tissue does not contain the mutations.

M. Ozturk et al. 1991.

p53 mutation in hepatocellular carcinoma after Aflatoxin exposure.

Lancet. 1991; 338: 1356–

Introduction & Objective

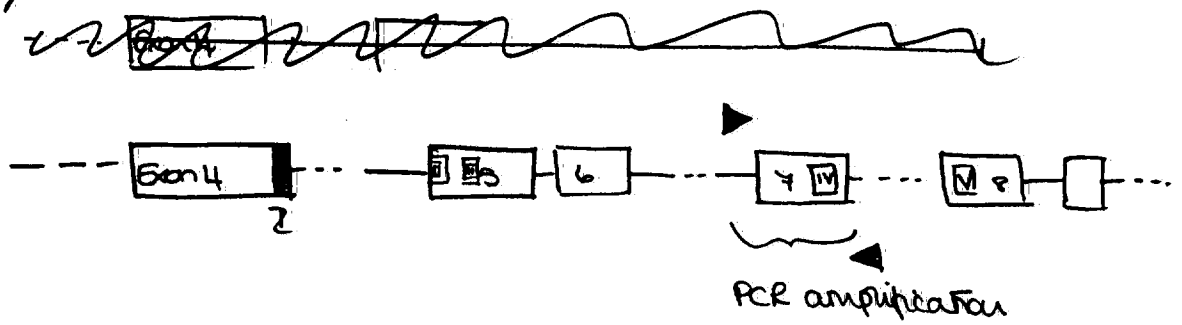
To investigate hepatocellular carcinoma associated with specific genetic changes in the p53 gene. ⇒ see refs 10/11
To investigate the frequency of codon 249 mutation in patients with HCCs from different countries and to test whether there is a causal relation between tumour-specific mutation and two suspected causal factors, hepatitis B virus (HBV) and Aflatoxins.

Methods.

167 HCC specimens – 122 fresh frozen
– 45 Paraffin embedded
taken from 14 different countries.

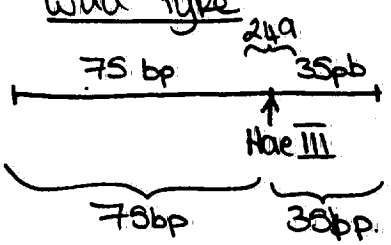
Genomic DNA
18 tumours = cDNA

p53 gene

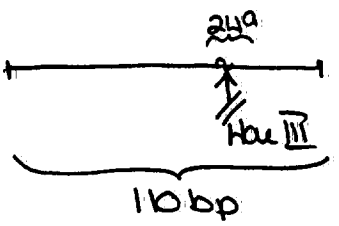


⇒ Exon 7 PCR products.

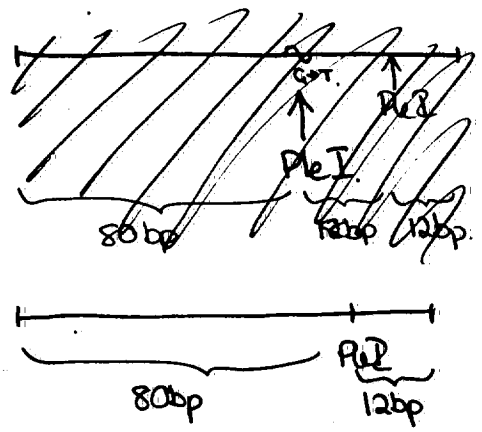
wild type

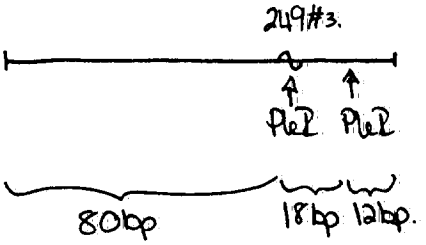


Mutant at 249



G-T at 249 #3.





Results

167 samples

12 = G→T at third base of Codon 249.

By Country:-	249mutn.	HCC Inc.	HBV.	Risk of Aflatoxin intake
Mozambique	8/15	109	11	High
Vietnam	1/3	10	10	High
China	2/30	20	16	High
S. A.	1/24	24	10	Low
S. Korea	0/5	18	5	...
Japan	0/12	36	2	L
USA	0/27	<10	0·3	L
Germany	0/20	<10	0·5	L
Spain	0/12	<10	1·0	L
Turkey	0/1	<10	1-5	L
Saudi Arabia	0/4	<10	1-5	L
Israel	0/3	<10	1-5	L
Italy	0/3	<10	1-5	L
India	0/1.	<10	1-5	H.

Authors suggest that heterogeneity is largely due to Aflatoxin exposure.

∴ Further studies in Mozambique & Transkei (SA).

15 Mo. } 26/27 = HBV exp 7/15 Mo } HBsAg +.
12 Tr. } 9/11 Tr } (active infect)

G-T at 249 in 9/27 patients
6/15 Mo (53%) 1/12 Tr. (8%)

∴ Mo 7x risk at 249 to Tr.
also Mo = 3-5x Hcc of Tr.

Both equally exposed to HBV. (11·2 % | 11·6 %)
Only known difference is in exposure to Aflatoxin.

Mozambique = avge 35 µg/kg - Max 1·5 mg/kg.

Transkei ≤ 16 µg/kg.

Van Rensburg estimated Moz. have 4x Aflatoxin B_1 to Tr.

similar findings in China.

Lehman, T.A. et al. 1991.

p53 Mutations, ras Mutations, and p53-Heat Shock 70 Protein Complexes in Human Lung Carcinoma Cell Lines.

Cancer Research 51, 4090-6.

*. "Not surprisingly, p53 mutations are now recognised as the most commonly found cancer related genetic change at the gene level (25)."

Certain mutant p53 proteins, but not wild type, form complexes with hsc 70. More extensive studies in murine cells indicate that p53-hsc 70 complexes are formed with proteins encoded by various p53 genes mutated between codons 66 & 232, and that binding to hsc 70 can be used to indicate the presence of mutant p53 proteins. However, Cannon & Lane recently demonstrated that hsc70 is not directly responsible for anchoring p53 in the cytoplasm.

Studies:- state of p53 in 9 human lung cancer lines by. ① Coimmunoppn of p53 & hsc-70
② immuno cytochemical staining
③ Nucleic acid sequencing of all 11 exons

to see corelⁿ between presence of muty & stable p53 hsc-70 comp.

Also looked at ras status in light of coop w p53.

"These studies address the hypothesis that muts in p53 and/or ras are required to obtain and maintain the neoplastic transformation of human bronchial epithelial cells."

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Hollstein et al.

p53 Mutations in Human Cancer.

Science; 1991; 253:-49-53.

Review focussing on the pattern of base-substitution mutations in the p53 gene observed in human cancers and their etiological implications.

Why? - 1.
N.B. endogenous & exogenous mutagens generate specific kinds of base substitution at certain preferred sites.
∴ may give an indication of origin of the tumours
2. Position of tumour mutations may help to define actn of p53 protein.

p53 - relevant features of the protein:

(i). several well conserved domains
(ii) ability to form complexes with viral & cellular proteins

Mammals, amphibians & bird = 5 highly conserved domains. 4 within exons 5 through 8.

Characteristics of mutation in p53:-

① 98% within 600bp codons 110-304.; exons 5-8 (mostly in exons)

② almost all somatic in origin
constitutive mutation may be present in <2% of cases.

③ 221/254 mutations at codons corresponding to conserved sequences. (human, rat, mouse, chicken Xenopus & fruit)

④ No single domain identified as responsible for maintaining p53 integrity.

⑤ Within mammalian p53 seqs 169/200 aa are the same in all spp. 248/252 missense mutations are at these sites.

p53 Mutations by Cancer Type.

"Mutational spectra" = ~~freq of~~ location and type of mutation in a specific sequence.

"Hot spots" = codons at which exceptionally high numbers of tumors have mutation.

By cancer "type" diffs in spectra w.r.t. "hot spot" positions and frequency of mutation type (transition transversion)

—11—

Egs.

Colon v. Breast

Epidemiology many similarities - but:-

① G:C ⇒ A:T transition = 79% colon. - ~~mostly~~ 67% at CpG sites in breast only 13% at CpG sites

② G:C ⇒ T:A = rare in colon. (0) - 23% in breast.

Lymphomas & Leukemias

CpG transition at 47%.

G:C ⇒ T:A = rare

A:T ⇒ G:C = 19% = common.

Lung & Esophageal.

G:C ⇒ T:A. (NSCLC) - all on nontranscribed (No strand bias on transitions)

for Oesophageal transversion occur at similar freq at G:C & A:T pairs. - usually A:T is rare.

HCC

Codon 249 G-T transition/transversion are represented

Origins of P53 Mutations

① - observation spectra differ in different human types - consistent with hypothesis that the origins of mutations are distinct in different human types.

These differences can be explained by

ⓐ diffs in metabolic capacities of diff tissues & cell types
ⓑ DNA repair diffs " " " " " "
ⓒ exogenous v. endogenous sources of mutation.
endogenous e.g.s - DNA polym. infidelity
depurination
Oxid. damage from free radicals.
deamination of 5 Me ~~Cytosine~~ cytosine
exogenous - specific DNA interactions.
✓ interruption of cell cycle / processes ⇒ ↑ "spontaneous" - type errors.

Specific mutations.

3 most notable features:-
(i) transitions in CpG dinucleotides contribute heavily to the mutation frequency in many cancers.
(ii) A mutation at codon-249 predominates in HCCs in individuals from high incidence regions.
(iii) There is a high frequency of non clustered G-T transversions in lung cancer.

(i) attributable to 5-Methylcytosine - sign of "spontaneous" mutation

(ii) blamed on Aflatoxin B_1.

(iii) could be blamed on cigarette smoke. - need comparison of smokers + non smokers!
N.B. also oxygen radical damage may ↑ risk.

"preferential mutation sites based on sequence context can be highly specific for different mutations and mutagenic processes."

Vogelstein & Kinzler.

Carcinogens leave fingerprints.

Nature. 355 p209-210
Jan. 1992.

The birth of a New science -
"MOLECULAR EPIDEMIOLOGY"

pin down suspects for ~~environmental~~ causation of cancer by environmental agents!

MOLECULAR EPIDEMIOLOGY = MARRIAGE.

EPIDEMIOLOGY	MOLECULAR GENETICS.
Association of Environmental factors with increased incidence of cancer -	identification of specific "tumor" genes - oncogenes tumour suppressor genes
No direct mechanism but Genotoxicity implicated	

∥

MOLECULAR EPIDEMIOLOGY

? Are these tumor genes the primary targets of these environmental agents ? ?

① "RAS" - as rodent carcinogens - base changes from simple mutagen assays - consistent

p21 ras protein - signal transduction.

(1) However in humans less success because

(a) not ubiquitous - not as frequent in all human tumours.

(b) only a few sites where mutation ⇒ oncogenesis

∴ limited comparisons.

∴

p53 Tumour suppressor genes.

= most common cancer-related genetic change

[Bennett etal 1991 (2)

Current data indicate that approximately half of the adult cancers of the lung breast, colon, esophagus, skin & other tissues contain p53 mutation]

= 53kd nuclear phosphoprotein = probable cell cycle regulatory activity.

"inactivation" = through mutation at numerous sites - point mutn, dels & insertion.

Specific carcinogen link. Hepato cellular Carcinoma

[Ozturk etal. 249. G-T transversion in HCC from specific regions. 249 codon changes linked with high HCC risk & high Aflatoxin intake. (3)
249 G-T rare in other cancers.]

Squamous Cell Carcinoma:- (4)

(Brash etal 1991.) p53

CC→TT double base changes = specific to U.V. in 23%.
100% at dipyrimidine sequence, 62% = C→T.
also characteristic of dipyrimidine dimer products of U.V.

other mutations = observed only at low frequency.

N.B. types of changes possible:

G:C → A:T; T:A ; C:G.
A:T → T:A ; G:C ; C:G

N.B. p210
"In future we may expect somatic mutations to point towards specific aetiological factors in cases where epidemiologists are unable to pinpoint specific agents.

+

P's remaining.

Are these agents Aflatoxin B, & UV also implicated in the other generic changes - or are they just the "last straw"

More Compelling Argument?

O2TUCK - REF. 3.
167 HCC specimens - sequenced. from 14 diff countries exon 7 only.
(RFLP)

BERSH et al. REF. 4. 24 tumours 14/24 = p53 mutn.

14/04/92.

Horsmans et al. Biomed & Pharmacother (1991) 45: 359-362.

Is there a link between debrisoquine oxidation phenotype and lung cancer susceptibility?

Table 1.

	EM.	P.M.
Control group (n=167)	155 (93%)	12 (7%)
Oat cell Carcinoma (n=32)	28 (87%)	4 (13%)
Squamous cell Carcinoma (n=41)	41 (100%)	0 (0).
Adenocarcinoma (n=10)	9 (90%)	1 (10%
Mixed and others (n=5)	5 (100%)	0 (0%

Conclude - does not support a role of PM. in LC. dupt.

—//—

Schäthal, A. The New Biologist. Vol 4(1). pp16-21 1991

OKADAIC ACID. —

p17. Differences from TPA.

TPA induce c-fos & c-jun transcription immediately - ↓ decrease after one hour.

OA ⇒ max 4 over several hours.

21/07/92.

GORROD PROPOSALS / REPORTS

① P.M projects -
"Comparative metabolism of secondary and tertiary aliphatic alkaloids, (George Aislaitner)

"The synthesis and biosynthesis of quaternary glucuronides of Tobacco alkaloids." M.C. Tsai.

Reports received from:-

(i) Yan Li on Cotinine Metabolites
(ii) M.C. Tsai on Quaternary glucuronids

No report from Aislaitner project

Li - Cotinine Metabolites. - no comment.

① successful synthesis of demethyl cotinine,
γ-(3-Pyridyl)-γ-oxo-butyric acid,
Demethylcotinine-N-oxide & γ-(3-Pyridyl)-γ-oxo-N-methyl butyramide

② determination of Partition Coefficients:-

③ separation cotinine from potential metabolites - work ongoing.

Tsai. - Glucuronides.

Guinea pig work. - failed to manage 4° glucuronides
∴ try Rabbits.

—

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23/07/92. NILSEN.

① Continue – long term / low level exposure.

② Low priority – a. How much NIH from own vs other peoples nuclei
b. How ensure abstainance.
c. How interpret no difference data
d.

$150,000 FP2 – no consultancy, no travel.
Basel?, Rome? ✓✓

Conrad – need invoices.

28/07/92

CORROD ∞ 44 71 836 3454

2 books – Chapman & Hall – have invited speaker
Medical Science Research – mail paper

RJR – invited to speak in Paris.

CTB paid –

① equipment – positively buying ? £8000 £13000
[£5000 in deficit –] – ask peter about.

② Invoice for 2 runs – 1 fare
1 contribution to Trans } not yet received?

③ Zurich workshop – The use & misuse of the dog in toxicology
"Zbinden" – very cheap = October 19th – 20th.
Funding for Jane Conrad – find out more info.

④ Visit 26th August? – ✓ Yes OK. book flights

⑤ Initiate work in Turkey – British PhD – in Turkey – Chemist interested in Metabolism – pharmacogenetics of nicotine handling – maintaining urine samples Istanbul – University Academic Dr Ulgen (Mert) – hard working – not brilliant
No background in nicotine – needs to work with someone in nicotine – George Schepers / Conrad. – Talk to Peter

⑥ Quaternary company Tom & Peter Crooks (Lexington) – invited
Talk to Peter

direct. – 071 333 4789 00 44 71 836 5454 x4789

20/08/92

① Telephone call to John Conrad – Please send invoices for all outstanding a.s.a.p.!!

② Dog Meeting in Zurich.

10:30p.m

Letter – instructing future invoices directly to ...

No go – Annie meeting –

27/08/92 Inbife

Nicotine in Hair

Method

Washing – SDS – comparison to normal shampooing.

Solubilise NaOH

Extraction diethylether/butyl acetate

GC with nitrogen-specific detection

Sample material

Conc of SDS compared to nicotine levels in permanent nicotine treated rat hair, mean 10 ug & 20 ug/day

% SDS	0	0.1	0.5	1.0	5.0	10.0
Rat	10	12	28	21	36	39
Nic. Seeded 10 ug/ml	18	19	26	24	28	31
20 ug/ml	21	28	26	25	31	30

} Nic ↓ by washing

Conc 80 ... 20

Rinse wp – 4 rinses.

Not completely consistent – washing effect even with pure water.

Included washing step which pres remove about 25% of nicotine but seems variable depending on material –

but Nilsen & Pahlsen do not wash before analysing.

Sites of nicotine – possibly through sebaceous labelling – Microradiographic

PG Exchange of binding of ... antibodies to nicotine in ...

Repeated washing – is there a limit to how much nicotine can be washed out

Comparison to metal ion data are ... similar & compartment models for nicotine.

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Solubilisation. same as 2 & N

1ml NaOH (5mol/l)
2h a [illegible]
3h ultrasonic bath

Extraction 2ml dichloromethane [illegible]
[illegible] shaking
(liq-liq extraction)

Phase separation - organic layer extracted, conc with nitrogen flow.

Analysis.

GC DB-FFAP (30m x 0.25mm diameter)

= very polar column - beginning there was interference with some rat hair (brown rat) : this problem was removed by using this column

internal standard = N-ethyl nornicotine

Recovery experiment - [illegible] of nicotine during extraction procedure

[illegible] for [illegible]

Detection limit 0.3ug/g - for a 30 mg sample

Corelation coeff v. good up to 140ug/g hair.

Recovery - free hair samples soaked in nicotine solution - related to amount found in hair ± 105%

Results from human hair samples... (Daniel [illegible])

Cig/day shows good dose response for non smokers to heavy smokers :- 20cig/day smoker - hair 27 ug/g - 3ug/g [illegible] [illegible] 20 cig/day - 44 ug/g [illegible] - bleached [illegible]

Segments of hair 3, 20, [illegible] cigs/day

0-2, 2-4, 4-6 etc etc. cm segments of hair

Same [illegible] but [illegible] 20 cig/day [illegible]

= bleached hair - approx every 2 months [illegible], suggests bleaching has an effect

Nicotine [illegible] cigarettes/day.

N.B [illegible] [illegible]/day [illegible] [illegible] 3 & 20cig/day [illegible] [illegible] but there [illegible] [illegible] characteristics

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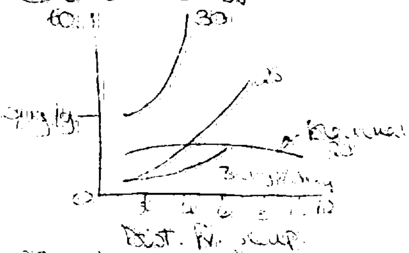
of the hair. Would investigate why there is this difference in the urine signal



Reasons the individuals to see how consistent this result may be

Could the difference be an inhalation of the 20 cig/day smoker in a non-inhaler - could explain the differences

Also need to look at a non-smoker to look at starting point

Possibly look at in vitro bleaching etc.

Metabolites

45 ug/day 125 ug/g (hair) 2 ug at /g ...

trace of 4.5 ..., nicotyrine, myosmine, nornicotine.

but cotinine may be external - ≈ 5% in smoke

Verify levels of cotinine in smoke

Animal studies

Brown Norway Rat (BN/CrlBR)

osmotic minipumps (model 2ML4) ... 4 weeks s.c.

hair growth - adult rat - hair growth v. unpredictable - patchy ... same days ... young rats - 3rd hair cycle - 60 ... day ... Rat should be at beginning of 3rd hair cycle = 60 days

dose 1 mg/kg/day.

based on ... et al (1991) ... mg/kg/day corresp to smoker 2 min after smoking (minipump)

Expt - 3 rats + nic. ... with control rat.

... (... to ... the ... + ...)

Harvesting of regrown hair at - 7 days - 2 rats
- ... - at 3.4 ...
- ... days - ... - distal + proximal

Urine collected at beginning + end

Blood samples taken at ...

Results. Nic treated = ... → ...

... = 0.2 → 0.4 ... - ...

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? Why such an ↑ in the last 10 days?

	Cage 1		Cage 2		Cage 3	
7			3.9	0.2	5.2	n.d
14	4.3	n.d.	4.4	0.3	5.6	n.d.
24	13.8	0.2	12.3	0.4	13.3	0.3

No difference in proximal and distal parts ∴ suggests no loss of systemic through hair growth

N.B. photographs of rats - hair regrowth always preceded by dark pigmentation

Nicotine conc in urine day 1 and sample day. - not much diff. cotinine in plasma - not able to say if reached desired dose

Plasma concns - not ideal but suspected lower than 30 ng/ml.

Performance of osmotic pumps.
Remaining at end

Nic	Nom	Actual	Vol.	Nom.	Actual
	14.8	27 mg.		700	740-770

Brown Norway Rat exposed to ETS - 'Rough & Ready' - Office of smoker.
found v. low nic conc in hair. 0.56, 0.67, 0.58. (4, 11, 17 days) with washing
without washing found 4 µg/g ∴ diff = huge with washing
but systemically exposed found no real difference with washing ∴ nicotine bound where it cannot be washed out.
also ETS exposed rats shows no increase in urine
(smoking ≏ 30 cigs/day in presence)
Could repeat latter experiment in more controlled way - conditioning room?

Future Activities?

- Mechanism -
  - external uptake to ETS & nicotine vapour
  - systemic uptake in albino hair
  - human hair uptake
- Confounding factors: color, thickness, age, washing, chem treatment UV exposure
- Interlaboratory comparison

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Conclusions - There is systemic uptake in the Rat.

?? in need of answer

Role of washing on hair.

Exposure of rat hair to ETS - when it is washed off.
when we measure b/t 10-14 days

Can we extrapolate systemic uptake in rats to humans
(quick calcns suggest from human data suggest uptake in humans may be totally diff. -)

Measuring issue - is it a real effect?
with [illegible] and [illegible] effect

What is the significance of systemic uptake for humans - if there is any. Extrap from rat data complicated - [illegible] exposure and [illegible] data suggests that it is not significant

Relevance of claims for extrapolation to [illegible] - Rat exposure not necessary for any further study.
Fashion of hair may have significant effect - from curves for hair length variation suggest could be 4x in difference in slope.

Repeat Rat study to prepare for publication? - but would patch expt be worth doing to establish [illegible] systemic contribution in humans
Patch may not achieve the peaks - .. try with cigarettes e.g. cig smoke from [illegible] premier.

2028541331

28/08/92. - Johan Organ. -

20+ ogs /day ⇒ 2x cataracts = 1/5 U.S Cataract cases

J.A.M.A. - 2 studies.

Editorial by Sheila West. - Editorial

Authors Dr. William G Christen
Susan E. Hankinson } 2 papers + editorial ?

Dr Robert Sperduto - National eye hospital says data contradicts this. two studies contradict them but additional 2 studies support it.

See Klaye, DE et al. 1989. 'Eye' 3(Pt) 349-354. S-31292-S

Cataracts and Cigarette Smoking. The City Eye Study
⇒ significant correlation RR = 1.0 ex, 2.6 ex heavy, 2.9 heavy.

QUATERLY REP.

Indoor Environment: 1992; 1: 300-307

Is there an adverse effect on the Intellectual Development of Children exposed to low levels of lead

Ann Spurgeon 1.00H

Nilsen

① Press - "ETS may be much less significant than we have been led to believe?"
Misclassification being generally favourably viewed by the Press.

② Publication - discussed previously - not yet started due to desire to complete 1 µg/m³ exposure

③ Concentration means = + 3 ?

④ 9 weeks - fall off - is this real - if so what significance would it have to the real life situation?

2028541332

⑤ high & low absorbers - what significance is there? - Does this not evade the whole issue?
Low or high appears to be linked to individual hair because remains the same with the in vivo exposure in an office

⑥ suggested paths to follow. - systemic v adsorptive studies
Mechanism of binding
long term one year exp.
Work to continue...

1989 Report
48 subjects - 12 sm ♂
12 sm ♀
12 Nsm ♂
12 Nsm ♀

Hair scalp outwards = ↓ conc gradient
Taken from both sides of head much the same
Hair washing = little difference
Sm. > NSm
Particle entrapment but ETS exp & NIC levels in hair

What shape?
-So what? other areas
How washed & when
levels of smokers
How meas ETS?

Raises following ideas for further Q's to be answered
Saturation - hair 'Quality'

Reproducibility non ETS exposure - removal of UE after 6 M.
Stability ⇒ Heat, Frost & U.V. = v. important.
Combination of internal & external sources?

Intro v. ext. Sources - cessation - tablets - + invest - need to estab. stability over time PUT

Rats - fed tablets in addition - but poss will cont. w urine etc.

Will there be a linear correlation with degree of ETS exp ∀ 0-20 cig
Dose resp - More people more groups

1992 Current Proposal negotiation
Publications planned: - linearity of nic adsorption with time & dose ① S.T. high ② L.T. low.
but - not really linear!! - be careful of publication.

2028541333

- Consequences of 'high' air/lab adsorbers for the use of nic as a marker –

(presumably this negates that)

- The sign of int distribution of nicotine.

But should stress that none of these are ready

Proposed work

① 1, 5, 20 & 200 μg/m³ – 12 months accumulation

(vapour phase)

What is the objective of this – how does it help us.

(1Y x 1 tech + 2m x Sci = 450,000 + 113,333 = 563,333 NOK + chem
= 650,000

② External v internal availability of nicotine.
Requires ethics committee approval –
What does it answer – Nicorette = not same profile as cigs
∴ cig max peak may apply.
How do avoid ETS exposure a control for differences?

3m x tech 2m x Sci = 112,500 + 133,333 = 245,833 NOK + Chems
800,000

③. Mechanisms of binding – EM
Electrophoretic separation
Corelly of protein, melanin etc etc
1YC Sci. 109,000 + + mat 900,000

④. Cotinine levels in subjects – why look for cotinine?
[illegible] if in very high levels (>10%) = also internal
but could also be external
2m x Tech (75,000 NOK)
Estimated total budg for 1 2 + 4 = 1000,000 NOK.

Comments:

① We have not got the answers to enough questions to push forward with dose monitoring using this method – indeed there is considerable evidence that there may be many reasons why this may not be so. I think our priority decision should be to investigate this – for this reason I believe the only useful proposals from Nilsen for 1993 are is

2028541334

① - pattern over 12 months - however characterising the nicotine vapour exposure in pubs a week of time at least until it is established as being a good model for ETS exposure. "Freshness" of TPM may have a significant effect on absorption & washing out etc.

Other than this I think that the most important fact to establish is how everyday lifestyle may effect the amount and distribution of nicotine -

e.g via U.V., frost, bleaching / chemical treatment
frequency of washing
Hair style
Hair characteristics

This should be relatively straightforward and should be viewed as essential before progressing any further with this project. [Once these factors are established it would be only possibly interesting to investigate the behaviour of hair with nicotine.]

As the cotinine experiment is so small and not cheap it may be worth doing - but unless cotinine levels are fairly high (& which you would possibly determine internal uptake) it will be difficult to interpret the results — could come from either source or internal Metabolism.

Publication should we try further to get some of his results into print - so that arguments for and against this process are in the public domain.

2028541335

03/09/92

Smoking and Cataracts.

0. Leske, M.C. et al. 1991. Arch. Ophth. 1991 109(2): 244-251. MEDLINE #4. p5. +EMBASE #4 p3	Case-control, 1380 participants. Lens opacities - smoking - OR 1.68.
② Playe, D.E. et al. 1989. EYE, 1989, 3(4): 379-384. MEDLINE #7. p7. EMBASE. #6 p6.	City eye study = 9 years prospective. 1029 volunteers, 54-64 yrs. Nuclear lens opacity: 2.6 part heavy 2.9. curr. heavy. "Data shows sign. assoc betw. Nucl. lens. opac. & smok. - heavy sm.
③ Harding, J.J. & Van Heyningen-R. 1989. Dev. Ophth. 1989; 17: 13-16. MEDLINE #8 p8.	No info = Beer & cigs as risk factors for Cataracts.
④ Moro, F. et al. 1989. Metab-Pediatr-Syst-Ophth. 1989. 12(1-3): 46-57. MEDLINE #9 p8. EMBASE #10 p9	Excessive smoking were considered - "AION our data seem to indicate that the onset of AION may be influenced more strongly from these risk factors than ageing."
⑤ West, -S et al. 1989. Arch. Ophthalm. 107(8) 1166-9. MEDLINE #10 p9. EMBASE #10 p8.	"The results suggest a significantly increased risk of pure nuclear opacities associated with cigarette smoking." Most smoking exposed. NO 1 with earlier age of start smoking.
⑥ West, -S et al. 1989. Arch Opthalm. 107(6): 875-9. Arch. Opthalm. 107(12) 1670-1 (comments) MEDLINE #11. p10.	Phakic subjects no evidence of ↑ risk w high levels of sunlight & no age-related degen. area w UV-B or UV-A exp. No mention of smoking other than as a key word. Contrary to ⑭ below.
⑦ Bochow, TW et al. 1989. Arch. Ophthalmol. 107(3) 369-72. MEDLINE #12 p11. EMBASE. #12 p10	Smoking & hypertension were not found to be PSC cataract risk factors. Data suggest that UV-B may be an important risk factor for PSC cataracts. (but contrary to above ⑥.
⑧ Harding J.J. & van Heyningen, R. 1988. Br. J. Ophthalm. 1988. 72(11) 804-14. MEDLINE #14 p13. +EMBASE #14. p12	Heavy smoking & beer drinking were associated with a raised risk. Aspirin like analgesics protect.
⑨. Racz-P & Erdohelyi, -A (1988) Ophthalmic-Res 1988 20(1) 10-3. MEDLINE #13 p13	Cadmium, Pb & Cu = 4 in cataractous lenses. "It is likely that the major source of cadmium is tobacco smoke while that of lead is exhaust gas of motor cars.

⑩ Klein, BE et al. 1985 Ophthalmology 1985 92(9):1191-6 MEDLINE #18 p16. EMBASE. #16. p14.	"In older onset persons.... smoking & lower diastolic blood pressure were significantly associated w greater prevalence of Cataract".
⑪ Tso, M.O. 1985 Ophthalmology 1985 92(5):628-35 MEDLINE #19 p17. EMBASE # 17 p15.	"The risk factors of senile macular degeneration included..... smoking"
⑫ Jain, I.S. et al. 1990. Afro-Asian - J. Ophthalmol. 1990 9/3:(91-92). EMBASE: # 1. p1.	TITLE:- "Black Cataract. A result of decreased ascorbic acid in chronic smoker."
⑬ ? GERIATRICS, 1991. 46(6): (24) ? ISSN - 0016-867X EMBASE #3 p2.	No details - Mentions smoking TITLE: "Drug use, other factors linked to Cataract use".
⑭ ? GERIATRICS, 1989. 44/12 (25). EMBASE. #7. p6.	TITLE: "Nuclear Cataracts associated with smoking"
⑮ ? J. AM. OSTEOPATH. ASS. 1989 89/11 (1449) EMBASE #8 p7.	TITLE: "Smoking may be a risk factor in developing cataracts".
⑯ van Heyningen, R & Harding, J. Br. J. Ophthalm, 1988: 72(11): 804-808. S&H. # 1/3/5. p1.	TITLE: "A case-control study of cataract in Oxfordshire: some risk factors".
⑰ Collman, G.W. et al. (1988) Am. J. Public. Hlth, 78(11): 1489-92. S&H 1/3/7 p2.	TITLE: "Sunlight and other risk factors for cataracts: An epidemiologic study."
⑱ Weale, S.K. (1991). Arch. Ophthalmol., 109: 196 (3). ANA BASE 2/3/4. p4.	Editorial. "Who develops cataracts"

2028541337

(19). Mohan, M. etal. Arch. Ophthalm. 1989: 107: 670-676 AMA BASE 2/3/9. p5.	TITLE: "Indian-US case control study of age-related cataracts."
(20) Hu, T-S. etal. Arch. Ophthalm. 1989: 107: 666-669. AMA BASE 10/3/2. p13.	TITLE:- "Age-related Cataract in the Tibet eye study."
(21). Lynn, M.J. etal. (1987). Arch. Ophthalm. 1987: 105: 42-51. AMA BASE 10/3/6.	TITLE:- "Factors affecting outcome & Predictability of Radial keratotomy in the PERK study." EXPEDITED PUBLICATION.
(22). Spencuto, R.D. (1986) Arch. Ophthalm. 1986: 104: 26-29. AMA BASE. 10/3/4.	TITLE:- "Systemic Hypertension & Age-related Maculopathy in the Framingham study."
(23). Miller, R. etal. (1982) Arch. Ophthalm. 1982: 100: 1060-2 AMA BASE. 10/3/8.	TITLE:- "Pseudoexfoliation, Intraocular Pressure, and Senile lens changes in a Population based survey".

2028541338

04/10/92. Schneider.

⇒ John Hessar on Monday 10:15.

Programme: Dbase.

surv

3rd method not available.

Multiple decrement life table

Select databases - a create!.

Age: Population: Total death. Causes of death.

—

Bayesian October 1st Seminar.

07/09/92. Staff meeting.

Fowler - 23rd September - ADA

Elder - 15th September + MC Nas 15/09/92 ANB.

25th - Formerai

Monday 14th - Meeting next 10:00

13th/14th October - Model. Swinstat/TNO

07/09/92

Chiba, M & Masironi, R. (1992)

"Toxic and trace elements in tobacco and tobacco smoke".

Bull. of WHO 70(2) 269-275 1992.

Aluminium conc range µg/g 600 - 1200

but

"In occupationally non-exposed male subjects, aluminium conc. were found to be 5 µg/l in urine, 4.2 µg/l in plasma and 1 µg/l in erythrocytes; these levels were not influenced by smoking or by age"

Arsenic <1 µg/g - virtually undetectable.

No assay of actual smoking - but. "On the other hand, a positive association was found between urinary As levels in children and parental smoking habits. The mean As level in the urine of children of non-smoking parents was 4.2 µg/g creatinine, in children with one parent smoking it was 5.5 µg/g, and in children with both parents smoking it was 13 µg/g creatinine"

2028541339

Cadmium

"Cd levels in the blood, urine & organs of occupationally non-exposed non-smokers are very low, but higher in smokers"

No really useful figures given of some studies regarding theoretical comparisons of smokers & non smokers

No real discussion of the potential consequences or no real criticism of the measured levels and their significance.

Kostic, C. - Report 1992.

Summary

1. A data-base of over 100 committees that recommend control procedures for various chemicals has been created, using Paradox 3.5 ("Bernard International")
2. Changes in occupational exposure limits for benzene were considered with respect to time, expert committee and country and were related to the existing toxicological databases.
3. Attempts were made to relate exposure of different spp. to CO and % COHb in the blood.

08/09/92

A.W. Katzenstein. (1992)

Environmental Tobacco Smoke and lung Cancer Risk: Epidemiology in relation to confounding factors

Environmental International 18: 341-345. 1992

Causes & reasons confounders:-

Occupations & occupational exposures -
bus, taxi & truck driving
vehicle driving or related

urban v rural dwelling

Genetic factors

Recurrent respiratory disease

Menstrual cycle 28 days

Red beans

fatty or fatty foods

fruit or vegetable product (& not)

Bit. coconut intake

2028541340

cooking fuels.

Combinations of these multiple risk factors may be even more important.

This paper criticizes the epidemiological studies on ETS for not considering sufficiently the confounding factors but in made really to predict whether these confounding factors may take away the observed risk.

N.S. cites a study by Fontham et al 1991 (Cancer Epidemiol. Biomarkers Prev 1: 35-43. 1991) which apparently collected data on sexual confounders but did not report on them. Without having reported on the data it is impossible to tell whether or not the confounders measured in this study could offer an alternative explanation to ETS use.

Shibata et al. (1992)

Dietary β-carotene, cigarette smoking and lung cancer in men.

Cancer Causes & Control. 3: 207-214. 92

"In conclusion the current analysis does not support the hypothesis that high β-carotene intake reduces lung cancer risk. Our report also demonstrates the importance of adjusting for cigarette smoking in the evaluation of the effects of dietary intake of β-carotene on risk of smoking-related cancers."

2028541341

09/09/92

In BfB - Nicotine in hair - proposals:

1. Washing: is there a continual decrease in washing? (Particularly for rats ets exposure!)
2. Gradient down the hair - should clarify the differences observed between the 4 subjects
3. In vitro hair treatment - bleaching? - does this have a significant effect - possibly look to other influences
4. Could we answer the question about the need for peaks? or how nicotine plasma concentration diurnal patterns may effect uptake.

10/09/92

Publications from Eastern Europe -

Bulgaria = BG.

[East Germany = DD]

Rumania = RU.

Poland. PL.

Hungary HU.

Russia - SU.

Yugoslavia - YU.

Cooper R. Smoking & Health in Russia & Eastern Europe

2028541342

11/09/92

From ASCA list: 26 Aug '92.

"Breast-Cancer and smoking, Vodka drinking and dietary habits - A case control study."

Pawlega, J. Acta Oncolo. 31(4): 387-392 1992.

Activities :- Scientific meeting; Project Management; Illicting Research

Functions :- Information Resource for informing approp. the bdiv of the scientific facts where & if appropriate

Advising on significance of scientific developments

either as trouble shooting or preemptively

S&T ACTIVITIES:

SCIENTIFIC ADVICE. ~~ADVISORY~~

PROJECT MANAGEMENT

CONSULTANTS

INFORMATION.

PRESENTATIONS

FUNCTIONS

(CENTRAL) SCIENTIFIC INFORMATION RESOURCE

TROUBLE SHOOTING

S&T COMMUNITY

Scientific Advice

Scientific advancement: Project management

Consultant programme

~~Scientific~~ [illegible].

Response:

2028541343

14/09/92.

MANAGEMENT OF INDOOR AIR QUALITY IN OFFICE BUILDINGS AND ENCLOSED PUBLIC SPACES:-

pl. para 2. In 50-60% of the sick buildings HVAC is responsible

p3- l4 - "But objections raised against the open-plan offices" --- Eg?

"Classic Bike" for J.P. → Highland Park

Grande Laboratoire - petite salle. 4ème. 13h30

Budget

[Find back for Govan!]

Particulates - general — Harvard Risk Evaluation

Francis Roe - Ind. Env. carcinogens + irritants/cell proliferation

Prague + Presentation on Benzene.

Documentation written by committee members

EPA Particles - C&B

Previous information on committees and acceptable risk.

Sunderland

Train ticket Les G-S-C Return. 60-00

(Hire car - await invoice!)

Plane ticket - 1520.

Taxi

O.Juice 1.39

Hotel. 85.60

Exchange. 1.50 comm

Taxi. 45.-. (Neuch ~~Car~~ → Les G-S-C.)

—∥—

22/09/92.

ETS: Joan Gray report:

NS Women exposed to husbands smoke have twice the risk of L.C. to N.S. women not so exposed = New study

University of South Florida to be published in next issue of JNCI.

210 LC lifelong non-smoking women; v. 301 NS - non L.C.

Heather. G. Stockwell

#

Staff Meeting. 20th 10:30 Addiction history

29th ISCSH.

30th - Schwarz, Schneider, Pages, Carchman.

1st 12:00 = Meeting Bayerman 6-7. New York. + Richmond?

6th BM Meeting

2028541345

23/09/92.
*Ring Bob & Richard arrange trip to Richmond?
*Arrange New Spanish lessons with Inlingua
*Expenses claim
*Write up Meeting with Kostic for Weed PSM & CDM.
*Send / chase up Harvard Ref f. Kostic.
*TNO Report. * Rosemary ask for Spanish S+H documents
* Spanish Presentation
*Nicotine Report.

23/09/92.
From Joan clay.
Study by Dr Dorit Carmelli, N.E.J.M. based on surveys of 4,775 sets of male twins. Some smoke because they have a genetic tendency to do so
Her study found evidence that genes play a role in whether people take up smoking, whether they smoked more than a pack a day or fewer than 10 cigarettes daily.
They found that 13% of identical twins had neither ever smoked compared to 7% fraternal and 39% of identical both smoked whereas

—//—

Tunstall Pedoe [illegible]
Non smokers 'exaggerate' effect of fumes
Articles in the independent
suggests that non smokers [illegible] to their [illegible] exposure exaggerating the amount of exposure and pulling on symptoms... however still maintains that ETS is implicated at least to some extent in heart disease.
Headlines –
Independent = "Non smokers 'exaggerate' effect of fumes"
Times – "Hazards of passive smoking 'exaggerated'"
⇒ "Passive smoking may be [illegible] than previously inflated..."
1 Peter has [illegible] in hand
Tunstall Pedoe [illegible] demonstrated that [illegible] who became ill have a tendency to claim [illegible] to ETS than those who are not ill. A bias [illegible]

2028541346

24/07/93

MOLECULAR EPIDEMIOLOGY

The bladder cancer story:-

'Black Tobacco & Cancer'. Introducing an Epidemiological Review
F Xavier Losch. & E Cardis. Lyon-France
Eur J Cancer, 27(11) 1345-1348 1991

Significance of Black tobacco compared to blond

"Countries where black tobacco consumption is, or has been, common tend to exhibit higher levels of bladder cancer incidence than do regions where blond tobacco is predominantly consumed"
= Observation ∴ what is the explanation.

In case control studies - black & blond appear to have diff patterns
"for bladder cancer for example, Vineis et al reported a relative risk of 9.0 for smokers of 20 cigarettes or more per day compared with relative risks of the order of 2.0 or 3.0 in studies carried out in the US., UK Japan or Canada These differences held even when taken into account the effects of occupational exposures & were subsequently confirmed by other studies'

Increased levels of urinal "potential" carcinogens in black tobacco smoke; blood & urine from black tobacco smokers. Particularly aromatic amines which may be linked to bladder cancer.

= Introduction of new species

follow up publication in same Journal

Also from EACR meeting -
Norsetti - from Turin, reported increasing evidence in the of angiosarcoma in bladder cancer from combined observation from the dye industry & black tobacco smokers

2028541347

24/09/92 S&T PLANNING PAC

Bladder Cancer -

* Legal responsibility to know the risks of the product? *
To update PM [redacted] on the changing face of the scientific · (written above the bar: Decision makers)
evidence about health effects of our product' -

- Duty of Care -

Diet

Presentation or Not?

Social acceptability, Dr Walder - Project proposal.

[No Euthan] [No SURPRISES!] [No END RUNS]

[No BULLSHIT!]

Mopsy - CSA New York - European Affairs
Who advises Mopsy on scientific aspects of the [illegible] in Europe

25/09/92

Telephone Mundy: -

28/09/92
Staff Meeting - Wed a.m. Tower meeting
16th - EMT meeting → [Note!!]

Agenda: Proposal, S&T role & interaction & possible future challenges
+ what else is happening in Europe

Modern [illegible] - overwhelming [illegible] [illegible] [illegible].
= [illegible] = [illegible]
[illegible] [illegible] [illegible] report on carcinogens (DHHS)

Colon Ca -

~~[illegible] [illegible] [illegible] [illegible] [illegible] [illegible]~~

Active smoking shows a risk of 3.4 but no observed risk for passive smoking.

Women & Smoking -
2 recent [illegible] - 1 in.

2028541318

30/09/92

Gregg Fowler / Tony Andrade -

Doses of hamsters:-

Age profiles

Heart disease + other associations

Petos statistics on cancer?

CVD

Evan Gregg CTS statistical confidence limits argument

Monica study Results - NY Nut.

Van den ~~Bircke~~ Brouck

also about N. Carolina nutrition meeting.

Barker - Southampton infant nutrition markers & correlation w LC & CHD

Benzene in water v. cigarette

2028541349

1/10/92 B.J.C.
RHD Seminars

Lad wei Conjugation D
Post + Refrhmonts, wine soft drinks, candies } price from Calumet
Farron Poe }
Jim Parry }

What ... of you ... on ... hypothesis
How does the bayesian approach affect the design of experimentation to test hypothesis?

—//—

Bayesian in hypothesis testing
Bayesian preference:-
Bayesian weighs how new evidence strengthens ... H

Bayesian measure for association between exp ... $Q(\theta_1, \theta_0/x$.-
But how does it weigh old evidence

—//—

Doug Spicer – Coresta Nicotine in ambient air
Experimental – situations not valid
This is most likely to be unreal in experimental conditions due to ... + dilution

2028541350

07/10/92.

① Richmond.

Meetings - European feedback to Richmond & N.Y.

Communication with Corporate Affairs CEMA - EEC ?

(Distribution of Fields & Tests in Neuch.)

See Hoe re Dang.

Dan Nebert NIEHS - Molecular Epidemiology

identify individuals with respect to Lic

Contact with David Greenberg in Brussels

prior to Mat Winnacker meeting in November

Responsible or prudent (NO)

Distrust for Unbifo

Dummy video conference prior to the 6th November

standards

Trip reports from Neuch ⇒ Richmond

Meetings twice yearly

Monthly reports.

Meeting 12/10/92.

Meeting reports from Mayada Logue - to be sent to Neuchâtel

Target:

Spanish lesson Nicole Dangel

Current projects -

① WOMEN & ETS/IAQ. IN 1993.

What are the health aspects of ETS specifically on Women.

Do the physiological diffs between ♂ & ♀ affect susceptibility.
(Is there a difference between ♂ & ♀).

Do the differences in incidence of LC & CHD amongst NS ♀ v ♂ reflect physiological differences or differences in exposure?

We would propose:-

① To find out the published differences
② To identify studies which look at diffs in physiology (for active & ETS)
③ To identify studies which look at diffs in exposure.
④ To identify areas where further research is needed to complete the picture (within 12 months)

Potential benefits

~~To~~ clarify the validity of ETS studies weighing heavily on women by highlighting confounding factors

~~To establish~~

In addition by highlighting confounding factors are would underline the overall toxic potential of IAQ environment (other than ETS)

~~To clarify the~~

---

② Children

Other areas which we would be 'up to date' with & would be available to provide a response to CA. when the issues arise (i.e areas we believe may come up in 1993) - but may not justify ~~adequate~~ further active project management.

13/10/92
Spanish lessons
Reply to Filipa
HER - presentation.
Expenses.

Ruig TAC - Gail Pollard - anymore newspaper cuttings on Ray Case?

13/IC/92.

① David Sassoon Am J. Respir. Cell. Mol. Biol. 7: 1-2 1992.

Hox Genes: A role for Tissue Development

Mammalian homeobox-containing genes (Hox genes) when by "homeotic mutations" ie. shifts in structures normally found in one portion to another during development. In mouse or chick embryos retinoic acid at physiologic mch can affect development and appears to act by regulating the Hox genes

"Although the current data are compelling for a general role of homeobox genes and RA as regulators of pattern formation in vertebrates, definitive proof awaits a more detailed analysis of homeotic function. In particular, very little is known about the specific mechanisms by which Hox genes mediate cellular activity for instance, since Hox genes encode nuclear transcription factors, what are the genes whose transcription is modulated?

E.C Candelora et al. (1992) Nutrition and Cancer, 17: 263-278

Dietary Intake and Risk of Lung Cancer in Women who Never Smoked.

Study designed to "evaluate the risks associated with lung cancer in women who had never smoked cigarettes. Dietary intake was measured and analysed, utilising a standardised food frequency questionnaire, to assess the contribution of various foods and specific micronutrients to the risk of developing lung cancer in NS. women".

Florida: histologically confirmed primary carcinoma of lung, NS

controls matched for age + race

Never smokers - <100 cigarettes or <6 months ever

2028541353

Telephone interview:-
demographic data.
residential history
participation in high risk ~~industry~~ occupation.
personal medical history
-family history of cancer & respiratory disease.

Diet - NCI food frequency questionnaire - revised version - 60 food items
= report over previous 5 years.
vitamin supplements over 20 years.
surrogate responses only required if lived with or participated in shopping and food preparation.

= 124 cases 263 controls.
65% personal } 57% personal }
31% telephone } 43% telephone }
4% mail.
64% adeno / 20% squamous
93% white 97% white.

? how valid is the dietary data?
Can they really separate out the food factors as main?

ORs associated with vegetable consumption were slightly higher after adjusting for fruit consumption but the decrease risk of lung cancer for the highest quartile remained the same.

Categories:
Vegetables
Green & Yellow Veg
Fruits
Citrus
Total carotene
β - Carotene
α - Carotene
Lutein
Cryptoxanthin
Lycopene
Retinol
vit A
vit C.

2028541354

self reporting generally shows higher R.R than Vit A from veg surveys only.

The conclusions are that there is a significant protective effect for lung cancer from the following:-

all vegetables ~~upper~~ 3 quartiles

Trichopoulos, D et al. 1992 JANA. 268 (13): 1697-1701

? what "correctable" confounding factors does this hope to address and how?

"Active and Passive Smoking and Pathological Indicators of Lung Cancer Risk in an Autopsy Study."

"lung specimens were examined without knowledge of the exposures of the particular subjects for pathological entities that are considered lung cancer risk indicators ...."

?On what bases are these factors linked to lung cancer?
?Why were non L.C deaths chosen?

400 specimens autopsied - 35 years and older - within 14 hrs of death
All greek from Attica - but could have been current or past residents from other areas

Each subject ⇒ 7+ blocks of tissue from main & lobar bronchi
5+ from parenchyma
≥ 20 cartilaginous bronchi & membranous bronchioles
+ blocks from scars and areas of fibrosis when present
2 histological segments from each block

283/400 suitable preps.

lung cancer risk indicators:- basal cell hyperplasia, squamous cell metaplasia, cell atypia } Epithelial possibly precancerous lesions "EPPL"

main + lobar + cartilagenous bronchi

+ mucous cell metaplasia
(membranous & bronchiolar/alveolar airways)

2028541355

Graded 0 when absent
1-3 (4) when present (4 = anyparently)

based on degree of change for hyperpnea + atypia
- extension around airway circumference Eos + Muc. metaplasia

sum of grade scores assessed as percentage of maximum possible

Reid index – RI ⇒ bronchial mucous gland enlargement =
(morphological counterpart of chronic bronchitis)
– Ratio of thickness of bronchial mucous glands (G) to bronchial wall (W) thickness.
1 = G/W ≤ 0.35, 2 = 0.35 < G/W ≤ 0.5, 3 = G/W > 0.5.
Index evaluated in 2 main bronchi + 5 lobar branches in each subject and mean value estimated.

Next of kin
206/283 interviews in person - spouse 43%
children 10%
siblings 6%
other relatives 6%
others 26%

RESULTS

Diagnosis		of 400	of 233	of 206
	CHD –	39%	60%	65%
	other CVD	10	12	10
	Digestive	6	6	5
	Genitourin.	1	1	1
	Accidents	15	16	16
	Unknown (not resp)	9	5	–
Age	≤ 39	1	1	2
	40-49	9	9	9
	50-59	19	20	19
	60-69	22	23	23
	70+	43	43	45
	Unknown	6	4	-

Gender	M.	69	72	70
	F.	29	28	30
	Unknown	2		

Interview data

structured questionnaires: - demographic characteristics
occupation - employment history
residential history
smoking habits collected
spouse
smoker or ex-smoker at time of diagnosis
age no cigs/day
every married person + spouse smoking also excluded

? what percentage of deceased when married + could reliable information on spousal smoking be obtained ?
? What about relatives/other family members who smoke?
? What about other sources of exposure air pollution, lifestyle etc?

Occupation classified as professionals
white blue-collar workers
agricultural workers
self-employed plus
commercial workers
employees
housekeepers

? How do these classifications help in assessing exposure to CTS as the "confounder"

Multiple regression results: EPPL as dependent variable
age, gender, smoking + residence - independent

① smoking:
EPPL sig ↑ in current smokers = no dose response
EPPL nonsig ↑ in past smokers - " " "
② gender:- EPPL sig ↑ in ♂ (with tobacco factor considered)
③ age EPPL ↑ nonsig wage
④ Residential history (crude air pollution index) ⇒ no corr.

ETS

62 of subjects 41 nonsmokers — husbands: 17 = ever smoke, 13 = never smokers, 11 = unknown.

~~17 married ever smoke husbands~~

"Nonsmoking women exposed to environmental tobacco smoke through their husbands had a significantly higher mean value of EPPL although the estimate was not precise. Thus, the difference (with the 95% confidence interval) was 27.88 (5.64 - 50.13), with a two tailed P of .02. Adjustment for one or more of the other variables indicated in table 3 & 4 had no effect"

For RI - no significant trends - but in general in expected direction, ing RI smokers > non-smokers, (to lesser extent ex-smokers to)
also RI urban > rural.
and RI ♀ married to smokers > non smokers

"the lack of association between occupation and lung pathology may be due to inadequate information on occupation"

N.B. higher values in smokers than ex-smokers suggesting at least that if connected to smoking this is reversible - it would be interesting to know over what kind of time scale!)

In effect the group within this study which were analysed for ETS were only 30 ♀., 17 of which married to husbands who smoke and 13 married to nonsmokers.
There is no breakdown given of these groups w.r.t. age, occupational history, air pollution etc although it was stated that "adjustment for one or more of the other variables indicated ... had no effect".
The diff. bet these two groups for EPPL was 27.88 (CI 5.64 - 50.13)
for current smokers it was 23.52. (CI 7.57 - 39.47)
The author explain this in terms of the comparison group (smokers compared to non-smokers with passive exposure)

Furthermore some smokers may have been excluded due to the fact that only non-rep cases were selected.

2028541358

This study is not as strong as it claims as there is very little actual passive smoke (30 subjects in total) and the power of the design to pick out the concievable confounders such as diet, air pollution, social status, living conditions etc is minimal to non existant.

Furthermore the 17 formerly exposed women were also classified as formerly exposed if their husbands were "ex-smokers" bearing in mind that there is no org. 4 in EPIC for ex-smokers it would be interesting to know how many of these 11 were married to ex-smokers rather than current smokers - and also, of the 30 women were any of these ex smokers? - surely it is likely that more of the women married to smokers were themselves ex or are now smokers?

Carl Brun Group re Molecular Epidemiology

A Carioli & R Puntoni (Athens IAQ meeting 1992)

DNA and Hemoglobin Adducts in People Exposed to ETS
A literature survey.

Purpose of paper = to review recent developments in the use macromolecular adducts in biomonitoring in molecular epidemiology studies highlighting those addressed to ETS exposure.
DNA adducts could be effective markers of exposure and be effective in predicting events leading to the appearance of cancer

Discussion
New, more efficient form of dosimetry avoiding the wide problems of extrapolation of animal results to humans.
Several studies failed to show correlation of PAH DNA adducts with active smoking often explained by background effects
Hb adducts however was ↑ in smokers v non smokers for C.T.S.
Perera (1987) 4-ABP-Hb, BAPt-BPDE-DNA adducts.
correlation with passive smoking only in 4 samples analysed
Note high PAH adducts due to charring - from many sources other than tobacco

No convincing links w ETS exp

Bartsch et al. 1990

type (air & flue) & number & bladder cancer inc 4-ABP-Hb

air > flue

4-ABP-Hb not indicative of ETS exposure

MacLure et al 1989

4ABP-Hb & non-smoker = 5 groups

Many weaknesses in the groups selected but some ↑ in 4-ABP-Hb in passive smokers - but little correlation with the cotinine measured

Hoz et al. 1990

DNA adducts in blood monocytes ^{32}P - identified changes for active smoking but not for passive

Pereira et al 1989

Molecular epidemiology - 81 lung cancer cases, 67 controls

No correlation of PAH-DNA for anything but smoking.

Hammond et al 1990

non-smoking & smoking pregnant women

4-ABP-Hb - at delivery. Passive smoking followed for first trimester.

Positive relationship w ETS exposure even after cigarettes removed.

Everson & Gallagher 1990

DNA - ^{32}P WBC, placental tissues & "lung cells" no diff bet smokers and non-smokers

ETS? - no data ∴ why was this included in the review?

Conclusions

① PAH-DNA cannot be reliable marker for active or passive smoking as there are too many alternative sources

② 4-ABP-Hb more promising but as yet no sufficiently rigorous study has been performed.

2028541360

15/10/12

B&M TRAINING

Work around - give reasons to audit notes separate from avenues
Stand still - don't sway - hands! - don't point fingers!
Dry throat - water
attracting attention of wayward audience - silence

Questions:

Pause
Reason
Example
Pause

People concern - public meeting isn't even on the list

Why are writers of public policy so concerned about making when public opinion isn't with it?

Is it true that EPA has based entirely on epidemiological "statistical" evidence
What about the "surrogate" measurement issue.

"There is more stuff coming off plastic down there will ever come off cigarettes"
A bit of a 'tall' statement

The ETS debate:
Proof vs Private EPA.
The "science" behind the ETS argument - statistics and Proof.

Be emphatic. Always have a 'hot' link
Drink water! - take breaths
explain terms

Tobacco based.
Not true to quote
surrounded "surrogate" story
Use of term "significant"

"for the results to be counted significant RR > 3.0"
Talks to the slides!

Very good use of avenues well clarified!
Who is Bernard Henin?

19/10/92

Associated Press Files.-

Jacksonville, Fl. 10/12/92 Possible genetic link to lung cancer will be examined to determine if there is any connection between the area's high fatality rate and a person's genes -

Dr Kevin Wolfe St Vincent's ~~Hospital~~ Medical Centre

Genetic study start [illegible] for [illegible] $750,000!

Genetic Scientist - Joan E. Bailey-Wilson [illegible]

WHO Weekly Epidemiological Record. 25 Sept 1992

Tobacco or Health: Tobacco Mortality: present and future

Annual death toll worldwide - 1m 1965 ⇒ ↑ 3m now

on present consumption would rise to 10m by mid 2020s

70% in developing countries

	1965	1995	2025
Devpd	0.9	2	~3
Devping	0.1-0.2	~1	~7

Devpd countries project rise of 50% over next 30 years

Much among women: U.S.A & U.K. ♂ ⇒ ♂

Moreover on current trends the annual smoking attributable mortality for females is expected to exceed that of males in the UK & USA sometime between 2005 & 2010.

From Tobacco Alert, July 1992; WHO Programme on Tobacco or Health

NB No citations for where or how these figures have been calculated

It is not known whether or not the figures from the developing world are taken directly by extrapolation from developed world which could be a source of error due to diffs in longevity & demographics society/age structure in the developing world.

Need to find out more about these figures to perform a stronger examination

2028541362

Future Terms de Visites:-

"Premier on Puritanism"

US a society of individualism is being overtaken by ritual conformism
Original puritan settlers advocated conformism - gradually rejected
true american dream - freedom, individualism etc
Now showing return to old puritanical beliefs
"New Puritanism"
Interview w Stephen N. Bolch - expressing concern for puritanical way
e.g.s of "New Puritanism"
Sex, wine, perfume, cigs, hair styles and party = out
Contraceptive even claim "unappropriate laughter" = out
New puritans start with harassment and further try to
impose laws to further their beliefs.
Phillippe Cole (L'express? - journalist?)

US product liability being abused by europeans as ludicrous
e.g. Car Park held responsible for death of a thief who died
following the theft of a car from their parking lot
implied - he died because he was allowed to steal it
ladder company sued for accident when someone fell off
ladder
Victor B. Appellate case - ruled as equally ridiculous??

Victor B. Schwartz = lawyer. Claims ultimately U.S will
allow common sense to prevail and people should follow their
common sense but not copy the unreasonable decisions (implied?)
How should we stop New Puritanism?
Ends on Quote
"To the puritan all things are impure"
D.H. Lawrence

2028541363

27/10/92 A PERSPECTIVE ON SCIENCE

(1) Alternative 'Health scare' slides RDC
Include "[illegible]" – [illegible] due to [illegible].

(2) Better examples of [illegible] – [illegible] [illegible] [illegible] (ANS)
– [illegible] [illegible] [illegible] a [illegible] etc.

[illegible] [illegible] [illegible] [illegible] [illegible] [illegible] of [illegible] [illegible].

(3) [illegible] quotes re "scientific" value of epidemiology. = RDE

(4) [illegible] – [illegible] [illegible] – [illegible] [illegible] headlines we have eg [illegible].
(1) Re health scares
(2) re [illegible] [illegible] from such health scares
CDM

(5) Alternative [illegible] surveys?

(6) Up-to-date statistics quotes to prove that this is still the case! – ANB

(7) [illegible] [illegible] re explanation of epidemiology, RR, – ANB

(8) [illegible] [illegible] [illegible] model – A [illegible] example? – RDE

(9) Alternative [illegible] for risk factor [illegible] [illegible] – RDC
(10) What is Relative Risk – ANB
(10) ETS [illegible] – Quotes from [illegible] [illegible] [illegible] [illegible] etc because [illegible] smoking [illegible] were not [illegible] sufficient [illegible] RDE

(11) [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] not [illegible] – [illegible] [illegible] [illegible] the [illegible] [illegible] [illegible] [illegible]

Quote from [illegible] – [illegible]

2028541364

RE shore, 1992. Reg. Tox & Pharm. 15, 180-221. 1992

"Epidemiologists need to give more attention to exposure assessment, because lack of quantitative exposure information is often the limiting factor that prevents the use of epidemiological data in QRA."

"Without an adequate exposure assessment, epidemiological studies have a limited value in risk assessment" and especially in QRA"

p207 - "A comparison of the common Models used for Dose-Response Evaluation".

Linear or one-hit model

One important criteria is whether the family of curves represented by a model contains enough flexibility to express the observed curvature in the data. The one-hit model always exhibits slightly downward curvature. Whenever it is fit to data that exhibit upward curvature, which is a frequent occurrence, this model will not fit well and is likely to overestimate risk in the low dose region (Crump, 1984). This is a poor choice of a model except when the data happen to be highly linear, because it has no flexibility compared to other maps.

[Kaisman - Talc tipping release - cigarette paper - Timetable
Cereal grounds. NTP. - inhalation study
Titanium - adenly.]

Cooked flavours - Maillard reaction - amino acids
Pyrolysed hydrogen.

[Denaturants in alcohol - [Methylene blue] - ~~[illegible]~~
FDA#4 - not legal in Germany
Sulfonator
Mixed to make]

[German Authorities out - Fraunhofer Tallotte N.W.
Reynolds Cin Foggin - technical information]

2028541365

20/10 '92

Aperos: Pizza [illegible] 1.50 a piece
Ramequin [illegible] 1.50 a piece
Pain Surprise 3.– par personne [illegible]
Canapé [illegible] piece
Feuilleté salé 4.50 [illegible]
Mini Sand. 2.– [illegible]
[illegible] 3.– [illegible] 60 x [illegible] SF200
Croissant au jambon 1.50 [illegible] piece x20 30.–

Drinks: Wine 5 cl x 5v. ? white SF12.60 red SF15.75
Beer x 20 ? ? 1.50/bottle [illegible]
Fruit juice x 20 ? small 1.80 [illegible] Pamplemousse 1.50
Water x 25 ? ½L = 1.20 1L = 1.80 SF 9.–
Coca ? ? small bottle 1.20 1L 2.30

} SF 250

[illegible]

Quotes from Gori & Mantel:–

Lung cancer Risk ~~factors~~ – use Gori & Mantel 1991 p.[illegible]

p.59.

"The exception (the causal role of ETS on LC) has been based not so much on admittedly questionable epidemiology, but on a public health stance of concern, driven by plausible but largely undocumented comparisons between ETS and MSS, and by an implausible assumption that no dose exists below which risks are nonexistent or unimportant"

2028541366

22/10/93

E.T.S PRESENTATION.

Suggestions:

① Health scare addition

Dioxin:-

1982, 2,400 people evacuated from Times Beach, Missouri (levels around 1 ppm)

1992 = levels thought to be safe taken away serious risk.

Over the years hundreds of millions of dollars have been spent in getting rid of dioxin which has earned its reputation as a killer because it is highly carcinogenic & causes high defects in mice exposed to small concentrations of 2,3,7,8- tetrachlorodibenzo-p-dioxin - a TCDD

More details are available on Dioxin - but you may find it a useful addition as it emphasises the "fusion" of new technical development to measure microscopically small concentrations and the Times Beach story shows how unguided "science" had to extreme suffering of over 2,000 people.

There are of course many examples of such 'health scare' reversals.

② Concentration examples - from HSA presentation:
To give a better idea of "concentration" which implies a volume effect and not just distance.

ⓐ Swimming Pool.

ⓑ Tea spoon

③ Remap a clearer "guide" from Huber et al 1992. to show how the scientific community recognises the change of the number they produce

"Relative risk relationships ... biological zone" ... pt

~~Stats~~ No, Undo but would emphasize

(4) Definition of Epidemiology:- — Statistical circumstantial evidence

"The study of the distribution of a disease in a human population and the factors that influence this distribution."

Relative Risk:-

"Rel. R. is most frequently expressed as a "Risk ratio", which is a calculated comparison of the rate of the disease studied in the exposed population divided by the rate of that disease ~~studied~~ in in some controlled population not exposed to the variable studied".

(8) Linear - No-Threshold = A better model ~~Threshold~~ ~~chromium~~?? X

(9) Microscope on cigarettes - Alternative could be to have a list of all the known risk factors as background - ?

(10) Add Mass Carcinogen quote:-

SG 1964

Tack Van Rose.

ETS debate chapter should include explanation of ETS.

2 main arguments - Linear threshold

Epidemiology - what it is - what wrong with it.

Current use of epidemiology as the investigative arm of ... which by ... the interaction of ? ...

Prof. ... to avoid the misuse of Risk factor, Statistics, Epidemiology, ... } ... ...

2028541368

26/10/92

Ask Bobabout projects proposals for 1993

28th HCA/HEE

13th, 16th, 23rd.

Molecular Epidemiology - prepare for Gian Cregg

Monthly Report - October.

Video conferences - Nov 6th - check w Clare

Peter ① Trondheim? -

② Expenses

③ Targets/revision

④ Wednesday - pm off

⑤ ICDA London Dec. 2nd.

London?

Manchester? 12.00 14.50

12.20 15.20

John Walker

11th / 13th

Computerised health care

in [illegible]

10/11/92

27/10/92

G.D Smith et al. (1992) Lancet 1992, 340: 709-12

Smoking as "independent" risk factor for suicide: Illustration of an artifact from observational epidemiology?

Excellent paper to highlight potential misuse of epidemiologically identified associations as causal.

L.S. Gold et al. 1992, Science, 258: 261 -

"Rodent Carcinogens: setting priorities."

trying to get animal testing results and risk assessment in perspective highlights the real consequences of overestimating risk.

2028541369

WHO, Geneva. See Praventmed, 1985; 14: 153-174.

Women & Tobacco: The first worldwide study:-

"Female smokers are more susceptible to infections of the ~~respiratory~~ tract and more likely to suffer duodenal & gastric ulcers. Menstrual disorders are also more common, onset of menopause is typically 2-3 years earlier among women who smoke & is linked to premature delivery, spontaneous abortion, fetal and perinatal death, and increased risk of delivering a low-birth-weight baby."

... etc etc.

"Last but not least, nicotine reduces the circulation of blood and the uptake of oxygen, with adverse effects on the skin, hair and eyes. (Contrary to the image provided in cigarette advertising, smoking causes premature wrinkles, bad breath, stained teeth and gingivitis, gum disease, dental problems & hoarse voice & chronic cough."

SOME WHO MORTALITY PREDICTIONS:-

From above article:-

"Death rates in women from lung cancer, a very reliable measure of the extent of the smoking epidemic, are rising virtually throughout the industrialised world. Over the next 30 years, tobacco related deaths among women will more than double, so that by the 2020, well over a million adult women will be dying every year from tobacco related illness".

Also from WHO - in Dr. H. Nakajima's opening address to the 5th World Conference on Tobacco & Health, 30 March 1987.
(Also in See Praventmed 1987; 16: 814)

"Over the past few years the movement to prevent & promote ill health has gained momentum", ... "yet still each year three million people die as a result of tobacco related diseases. It is projected that, if control measures on a wider scale are not undertaken urgently within the next few decades the annual death rate will be ten million".

| spread. | b+enter |

Are there two quotes consistent with

(a) each other ?

(b) known proportional smoking statistics for men & women ?

(c) WHO or Tobacco product market increases/changes over the next few decades ?

—//—

Wolf Reininghaus -

(1) Copy of application to ethics committee

(2) Visit to discuss progress

(3) - Muller -

inhalation studies

Any "interesting developments" re Mouchel [illegible] assays

Muller free radical damage assays with Alt elution.

comparative studies with [illegible]

& aldehydes, etc etc

Tanner also?

Prof Note re [illegible] --

2028541371

29/10/92

Ulf Landegren

Detection of Mutations in Human DNA.

General information on methodologies used for detection of DNA mutations.

N.B p3

"The recently elucidated mutation causing the fragile X syndrome is characterised by an increased copynumber of a particular repeated sequence $(CCG)_n$ [4,5]. Hereditary mutator DNA of this type may prove to be a more general phenomenon in human disease(6)"

Refs cited

4. Annerwalla, J., Verkerk, M., Pieretti, M. et al. Cell 1991 65: 905-914
5. Brewer, E.J., Pritchard M Lynch M et al. Science 252: 1711-1714 1991
6. Sutherland GR, Hoar EA, Brewer E et al Lancet 338, 289-292, 1991

Highly controlled or compulsive use (: control, withdrawal)

Definition of heroin use, cocaine use, opioid addiction to perception

No control from smokers for definition - No means of treating
Accumulation of nicotine from TTS cannulas & sequential use?

02/11/92

Bernadette Healy NIH sent Letter - to volunteer organizations

B.S. Hulka - General Concepts in Molecular Epidemiology

(Biological Markers in Epidemiology - Ed. Hulka)

For large RR - historically didn't need to understand mechanism

Now - molecular biology important for smaller RR

Transitional epidemiological studies - obs studies w markers

- small sample size - large differences between groups

"Misclassification" - e.g. Passive smoking - cotinine in urine

Design and analysis - costly

Involvement of bio markers in epid studies - collab. diffs

"Scientists" vs "Epidemiologists"

"Significant" environmental exposures - eg long. of exposures

[illegible] of findings geographically & interlabs

Why? Return

Improve accuracy & ↓ misclassification

Preclinical disease improve prognosis

disease classification - intervened diffs effects

"Risk assessment" - [illegible] rather than reality [illegible]

Scientific increase credibility of weak associations

eg EMF - true effects or not

- mechanisms - causes of disease & etiology

Franco Merlo:- Review of human studies

Complications between exposure & adduct level

Complexities of genetic contribution v external influences

Getting prevention in proportion tobacco / alcohol = 100% prevent

but, food, workplace, [illegible] & UV not

eg smoking - smokers

ex no

non smokers

"inverted smokers"

} Questionnaire; cotinine

2028541374

also occupational exposures – coke oven etc.

Hb studies – adducts mam w smokers, nonsmokers = 4

Phenotypic metabolic diffs = acetylation

Cyp1A1 – high ind = cancer risk

also GSTu activity

Other cancers Glutathione S transferase activity ... UCAC

Oncogenes & Tumor suppressor genes –

Stefano Bonassi Italian Databank and Ida Gorden

Relationship between biol markers & steps along "disease" pathway

Databank.

4000 = 5000 subjects/cohort – = number of diff cohorts"

1.5 = ... capable of pooling with ... etc ...

what of the 1.3?"

diffs bet labs. –11

EXTRA

Or ...?

Californian Data bank. – familial ovarian cancer

Perera Biological Markers relevance to lung Carcinogenesis

Validation of biomarkers = Rel bet Bm & exp. – interindividual vari

... exp

PAH, – Cig smoke Rel. to cancer Risk Predictive value of markers

Workplace

Ambient air Pollution

Susceptibilities = High P450; low GSTm1 act, Low β-carotene

[G:C→T:A in ras] PAH – specific?

Smoking – PAH-DNA adducts + lymphocytes = Elisa immunoassays

< 80% ND – nondetectable adducts – of 70% smokers

cig smoking is assoc w PAH adducts in lymph.

Vit: pot effects – weak ...

2028541375

foundry workers RR 2-6

Air pollution -

correlation of markers between polluted industrial areas in poland to rural areas - also then relate to LC risk

correlation between markers

conclude - ability of whether to environmental exposures show interindividual variability & helps show why

25 year study with sample banking to look at markers before development of cancer!

Quantitative RA. ?

Surrogate material for target tissue

Dr Riccardo Puntoni

Biomarkers of carcinogenic exposure & Risk

Biomarker monitoring DNA adducts

Blind study No group diff in DNA add, SCEs ? no great diff

Micronucleated cells - ↑ in Group B.

supported with studies in animals

Giorgio Assennato DNA adducts in coke oven workers

1987 - steel plants - chest x rays, cytology etc - no results.

N.B. Multiple exposure to complex mixtures

Machine operators show highest levels of DNA adducts - surprisingly not topside workers supposed to have higher exp

$\mu g/m^3$ exp

Lavage studies - or expectorant of - faecal/mucosa provide enzyme info for colon cancer could expectorant system to examine for lung

2028541376

1.5 increase of RR for overall multiple cancer risk
? acceptable cancer risk ⇒ 1.5 2.0 <3.0 ?

GASTRIC CARCINOGENESIS

Chair: Carlo La Vecchia

Eva Buiatti - Stomach cancer in Italy (Published)

Case-control study.
Central Italy - high risk - Genoa & Cuneo - low risk (based on mort data)
Questionnaire - food consumption
Protective fruits - onion + garlic & spices Raw veg - the effects
Risk factors - "traditional soups" = reheated mixed soups
Meats
Independent effects of each food group
by food nutrient specific intake -
Risk - by Person but not nutrient
but all Ascorbic acid > ~~Beta-Carotene~~ > ~~Fat~~ β-carotene
↓ protective effect
Cancellation of intake of protective & risk factors in the same

Dr William Blot ~~Date~~ Study of gastric precancerous lesions -

China - CC study of stomach cancer.
25% of gastric cancer deaths in the world!!
Shandong Province high risk area > Japan (old)
higher than Japan
(what about local effects in Japan?)

Med assess w/ cig smoke -
(Alcohol?)
Protective effects for fruit & vegs

Results - negative assocn - v strong.

Study 1989-1995 - Precancerous Gastric lesions study of their determinants & rates of conversion in a pop of China at high risk of stomach cancer.

Age 35-64 entire popn 4,389
histologic data on 83% 3,433 (Endoscopic-examination)
superficial Gastritis
chronic aspetic Gastritis
Intestinal Metaplasia / large bowel
Dysplasia
Gastric Cancer
Men > women but most significant in IM/Dys/GC
Cigarettes 1-19 OR 1.5 - 2-0-2.0 95% CI
Cigarettes smoking almost entirely accounts for diff in metaplasia in men & women

Alcohol intake

Domenico Palli Genetic studies Gastric Cancer

CSTI phenotype - zanghieri et al. Cancer Lett
Familial Occurrence of Gastric Carcinogenesis
La Vecchia study
How do they consider separation between familial & sporadic?
→ 34 K ras Mutations

Pelayo Correa - Mechanisms of gastric carcinogenesis (Louisiana)
p53 immunochemical abnormality
hyp-met
3rd candidate - Cigarette smoke

Bld Alcohol not as much as cigarettes when adjusted
Effect is weak but possible

Pesticides, Dioxins & Cancer Risk.
Giorgio Assennato

Pier Alberto Bertazzi (Milan) Cancer effects of human dioxin-exposed subjects.

Seveso - industrial accident/long term effects on susceptibility
Zone v cont v No of persons
Dramatic effects - chloracne

Values as high as 56,000 ppt in serum (TCDD level in chloracne cases)
Risk for haematopoietic cancers
General hypothesis - interindividual variation reg TCDD receptor.

High affinity binding to Ah receptor + hsp90
+ cant → nucleus
Dioxin responsive elements in DNA - DRE → P450IA1.

TCDD - internal dose
Ah receptor measured
and arnt gene - alteration may → ↓ resistance
Polymorphism of cyp1A1 gene + product.

Compare diffs bet chloracne + nonchloracne (or same people) planned
same hypothesis on cancer
Pilot study - 20 studies
EROD activity - w cyp1a1 genotype (CYP1A1 genotyping)
Compared after induction of TCDD

- NIEHS - RTP
George Lucier, Lab studies of dioxin & cancer risk: implications for risk assessment

Dioxin-like compounds TCDD = most potent
Biochemical changes mediated through Ah gene battery
Biological responses CANCER - Devel - 7 animal studies - all toc
multisite - both sexes but site diffs bet sexes
also - developmental, Reproductive & endocrine toxicity
Immunotoxicity, cell proliferation, wasting syndrome

- receptor mediated carcinogenesis (Ah receptor)
No TCDD-DNA adducts --ve in STT for genetic tox
Tumour promoter in 2 stage models liver & skin - Mechanisms not known

Risk assessment - acceptable risk ADI = 10 pg/kg/day Canada 10^{-3} for USA

depending on whether linear dose model or threshold model is taken
Linear rel bet exp & response even in low dose region
Le cell proliferation = not as classic ! except low doses !
Considerable amount of uncertainty remains concerning these

Tuesday 3rd Nov
PHARMACOGENETICS + CANCER RISK
Silvia Franceschi . Chair.
~~Neil Caporaso (NCI)~~ - Pharmacogenetic markers of suscep. to common cancers

Lung cancer risk associated with carcinogen detoxifying enzyme activity - S. Petruzzelli (Pisa)

BP - Epoxide - EH ⇒ diolepoxides = carcin
Glutathione conjugation + 1 dea = harmless
(AHH)
What are enzymatic & genetic determinants of balance bet car v detoxifying events & how differ between people
GST -
AHH, ECDE, EH, UDPGT ~~[illegible]~~ induced by smoking
GST & GSH depressed by smoking
CYP1A1 higher in smokers (due to AH induction?)

GST activity lower heavy smokers & LC cases

Seasonal variation in smokers (Perera) for DNA adducts - here showed reflection - inverse rel w GST & pos rel w AHH.
Correln of AHH w DNA adducts in smokers but not in NS
AHH = marker for DNA damage [* Any discussion w Perera re mixed pops not smokers !]

2028541380

Ratio of AHH + GST might give a better predictor for L.C.

Neil Caporaso - Pharmacogenetic markers of susceptibility to common cancers

Many of exposures are "absolute" causes (ie Tobacco) only 1:8 smokers develop L.C
Chromosomal ab + cancer. but only 2% have clear
heredity - (8)
Familial aggregations - chance / Exp / Herd / Gene-environment
Pharmacogenetics = unusual drug responses with genetic bases
eg Primaquine + G6PD def ⇒ haemolytic anemia
P450s - re cancer.
1A1 + 1A2 ⇒ lung C. etc
also debrisoquine but actual association inconsistent (re NNK & nicotine
= very controversial)

Genetic risk in lung cancer
10% poor metabolisers Debrisoquine = genetic control

Adeno carcinoma shows no relationship with deb phenotype
Deb metab ratio - Δ(ur)
Cyp2D6 - affected by other medications
Prevalence of deficient metabolisers amongst popns (about Jap + Chin)
Cyp1A1 - Caucs - 2% Jap - 24%
⇒ lung cancer risk
eg Prostate cancer Black White Orient
highest lowest

but have matched twin pairs

PG associations are plausible but as yet equivocal evidence
remains mixed
No single trait likely to be determinant
Methodology must improve

M.T. Landi
Aromatic Amines etc & Bladder Cancer Risk.

Hypoth: - The assoc of cig smk on Blad Canc can be explained by aromatic amines - genetic based metabolic diffs could show suscep diffs

Internal dose - Nic, Cot + urine mut (+ questionnaire for cancer)
Bid markers - 4AB protein + DNA adducts

100 Healthy - 50 NS 50 S. 31 black
16 blond
4 pipe

Mutag = corel to Hb-4-Ab
Black > blond
dose response -

N acetyl transferase phenotype - highest Hb adducts in slow acetylators and smokers

Saturation
slow acet ⇒ higher Hb add.
Saturation mechanism at Nic/Cot 15-20 (Nic/creat)
for slow Ac & FOX.

Only a few subjects w complete concop bet phenot + genotype

N.sig diffs.

Dr Richard Hayes - suscep to Benzidine exh evidence

Aromatic amine Metabolism - acetylation = protect
oxidation - active.

∴ slow acety = ↑ RISK for bladder canc
RR varies from 17 to 2 !!! Heterogeneity!

Benzidine - metab subs diff from other aromatic amines due to 2 ~~amino~~ amine groups
China - 3 cities benzidine workers - follow up programme
cohort incidence study - 30 BC cases

↑3 fold risk assoc w tobacco
Dose resp - overall BC risk = 25

2028541382

Bochum studies.

38 lung exposed cases } Matched age + city.
43 exposed controls }

Dapsone dose - for phenotype ascertainment
also genotype analysis

	Phen		Gen NAT2	
	F	S	0-1	2
Case	34	3	33	5
Cont.	33	10	33	10
RR	0.4		0.5	
	0.1-1.3		0.1-1.3	

Slow acetylation may even be protective for benzidine exp.

Summary - Studies in China show excess risk of BC from benzidine exposure but no excess in slow metabolisers

Nathaniel Rothman - Method. considerations in Pt. studies

Assays - ready for use - accuracy - what impact does bias on crude estimates

The impact of Met. phen & genotype misclassification

NCI studies over last few years eg Bladder cancer - NAT
lung cancer - Cyp2D6
+ few in progress

Misclassification does occur - what is its impact?

Sources - various

Sensit ++

Spec. --

Determinants of bias on odds Ratio - influenced by Spec, Sens,

Prevalence of Risk factor & Magnitude of odds ratio -

take impact of debrisoquine phenotype misclassification 9% screening 100% spec. but various sens

Sens.	observed OR.
100%	10.0
99%	9.9
95%	2.5

would be very careful of the digits in the 1st because they could be explained by misclassification

Angelo-Pereira dur
M. Study.

HIV wh prevalence varies but sen = 90%

Country	Prev	True OK = 10 Observed OK
China	10	9.1
USA	50	5.5
N. Africa	90	1.9

} Misclassification = causes of these
} dyps - not demographic factors

Assays not yet ready to decide what is appropriate

CANCER-PRONE FAMILIES & SUSCEPTIBILITY GENES

PETER BOYLE - CHAIR

Lisa Diller - Germline p53 Mutns in Li-Fraumeni syndrome
(Dana-Farber Cancer Inst)

Heritable mutant p53 assoc syndromes
Li-Fraumeni syndrome - 50 - 85% assoc w p53 mutn
Cancer prevention for gen at risk.
Retinoblastoma - because early impact - monitoring during
high risk period = early identification - good assoc

Li-Fraumeni - not so simple
p53 predictive testing - major advantage - identify non-carriers
Carriers = chemoprevention? = future =
Risks of P53 ident.

Pierotti, Marco (Milan) Mutations in heritable & sporadic cancers
(not like abstract)

Role of p53 - as early or late event
Lung tumour suscept gene in mouse model.
Bronchial dysplasia - rare but assoc w multiple lung tum
del chr 17 p13 - v early event before other chr dyps in tumours
Thyroid - p53 - late event - event of progression
Spectrum of mutation could be informative - in late event
Thyroid nearly all = frameshift (deletion) v few mutation

2028541384

- Mice :- more useful model
Many conserved sequences - may have same susceptibility loci
Mouse & human lung adenocarcinomas have many similarities

Mouse chr 6 - (near K-ras2) suggest human chr 12p12 for possible linkage to adenocarcinoma

Diff in aggression bet male & diff thyroid cancer - p53 gene may show link between bdb & epidemiology in general

P Singini [Geneva] Immunologic factors in cancer predisposition
Genetic syndromes prone to cancer - Downs syndrome
[Bloom telangiectasia
Fanconi anaemia]

Transient leukemia seen unusually
assoc. w +21 even in non DS.
Mapping of transient leukemia gene

Heterozygous Ataxia associated w high Breast Cancer.
Also possibly with radiation (e.g. mammographs) = ↑ risk

Approach - Genetic counselling - smoking crop not to employ
that can be generally at reduced risk for smoking.

It is possibly true to say that the world would be a "better" / "healthier" place if there was no 'perceived cosmetic' benefits to smoking encouraging people to smoke - however this is not the case - for many people smoking / non-smoking is perceived as beneficial therefore it is important to allow that personal decision whether or not that is correct is a matter, & should be a matter for considerable debate.

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09/11/92

Wendy Burrell - 00 1 914 335 9217 - not in will call back!

Conference summary:-

The general trend in epidemiology in recent years has been to try and improve the "classical" epidemiological studies using molecular biological techniques ~~to improve on this to evaluate~~ to clarify exposure levels and ~~not~~ "biological doses". Thus biological markers are increasingly being looked for which ~~may~~ ~~validate~~ are thought to represent real individual exposure levels more accurately than ~~atmospheric~~ external measurements (eg atmospheric, dietary etc.) Barbara Hulka, (University of North Carolina) described how biomarkers such as cotinine had proved useful in resolving problems of misclassification in passive smoking studies. ~~Other biological markers frequently being used in such "molecular epidemiology" studies include DNA adducts and Hb adducts for various compounds, (most notably with Polycyclic aromatic hydrocarbons & aromatic amines).~~ The most popular biological markers for exposure looked for are DNA & protein adducts, (eg. Haemoglobin adducts) and it is quite rightly argued that one of the virtues of such markers is that they give an ~~idea~~ of direct measurement of biological dose - particularly in the case of DNA adducts whereby the actual activity of the carcinogens which do bind to DNA are carcinogenic by virtue of this binding activity. However there are problems. ~~There are many factors which affect the binding of chemicals within the cells~~ There are complications in extrapolating external dose from biological markers due to many factors of either genetic constitution or external influences, (eg. phenotypic metabolic differences & dietary factors), as was discussed by several speakers, (Franco Merlo, (Genova; Federica Perera, Columbia University N.Y.) Peruzzotti, (Pisa; Caporaso, NCI Bethesda; Kanai, Milan;

10/11/92 - John Warren
Mark Gundelar - Strathclyde - pharmaceutical sciences.
(+ J Gabrielsson)

Scheepers - publication problems -
Chapman & Hall by end of next week + 4-6 months

Short publications - Journal Med Sci. Research - suppl. - early 1993.

Jiri Damani.
The Queen's Uni. N.I., Fax 962 603 6296.
Dpt Pharmacy.

"Nicotine group" - pure science worker nicotine. - meeting towards end '93?
Proposal
Positron emission tomography - regional activity of nicotine in brain.
Metabolism of nicotine in brain.
Increase in whole body metabolism after smoking - but no knowledge of regional variations.
Other techniques - NMR. + spectroscopy identify conc of compounds in brain.

Hb = reduced Hb - conc. in ferric ions (= paramagnetic ∴ resonance)
↑ Brain activity ⇒ reduction in reduced Hb in venous side presumably due to overcompensation of increased metabolism

Dr Jens Frahm (Max Planck, Göttingen) - Early February -
Implication mapping centres of brain activity - implication re treatment with alzheimers & Parkinsons: -
(Could turn now + for alz / Park disease research?)

Problem can't determine flow ∴ changes could be due to increased flow or reduced oxygen uptake!!

Report back after February - possible further proposal.

Nordberg etal, Alzheimers disease. Basic Mech + Therap. Strat.
66. Brain Nic Rec. deficits in Alz pat. as mapped by PET techniques.
1991 - J Wiley
Biol. Psychiatry, 2: G. Raccagni et al Eds. 1991 Elsevier.
Nic rec deficits in Alz. Pat. A possible diagnostic marker